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I, LEANNE MYNOTT, MANAGER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003907110 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD. as filed on 22 December 2003.

WITNESS my hand this
Seventeenth day of November 2004

LEANNE MYNOTT
MANAGER EXAMINATION SUPPORT
AND SALES

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Regulation 3.2

Fujisawa Pharmaceutical Co., Ltd.

AUSTRALIA

Patents Act 1990

PROVISIONAL SPECIFICATION

for the invention entitled:

"Ornithine Derivatives as Prostaglandin E2 Agonists or Antagonists"

The invention is described in the following statement:

DESCRIPTION

ORNITHINE DERIVATIVES AS PROSTAGLANDIN E2 AGONISTS OR ANTAGONISTS

TECHNICAL FIELD

This invention relates to new ornithine derivatives and pharmaceutically acceptable salts thereof which are useful as prostaglandin E_2 (hereinafter described as PGE_2) agonist or antagonist.

Moreover, this invention relates to a pharmaceutical composition comprising the above-mentioned derivatives or pharmaceutically acceptable salts thereof as an active ingredient, a method for treatment and/or prevention of PGE_2 mediated diseases, a use of the above derivatives, and a process for preparing thereof.

BACKGROUND ART

PGE_2 is known as one of the metabolites in an arachidonate cascade. And it is also known that it has various activities such as pain inducing activity, pro or anti-inflammatory activity, uterine contractile activity, a promoting effect on digestive peristalsis, an awaking activity, a suppressive effect on gastric acid secretion, hypotensive activity, platelet inhibition activity, bone-resorbing activity, angiogenic activity, or the like.

PGE_2-sensitive receptors have been sub-divided into four subtypes, EP1, EP2, EP3 and EP4, and these receptors have a wide distribution in various tissues. The effects associated with EP1 receptor activator are believed to be mediated by mobilization of Ca^{2+} from intracellular stores. The EP3 receptor is an example of promiscuous receptor that may couple to different second-messenger systems. Further, the effects associated with EP2 and EP4 receptors activator may be considered as inhibitory, and are believed to be associated with

a stimulation of adenylate cyclase and an increase in levels of intracellular cyclic AMP. Especially, EP4 receptor may be considered to be associated with smooth muscle relaxation, anti-inflammatory or pro-inflammatory activities, lymphocyte differentiation, antiallergic activities, kidney dysfunction, mesangial cell relaxation or proliferation, gastric or enteric mucus secretion, or the like.

Therefore, PGE_2 receptor blockers (in other words, PGE_2 antagonists), particularly EP4 receptor blockers possess binding activities to PGE_2-sensitive receptors, specifically to EP4 receptor, therefore they possess a PGE_2-antagonizing or PGE_2-inhibiting activity. Therefore, they are expected as a medicament to treat and prevent a PGE_2 mediated disease, especially a EP4 receptors-mediated disease, such as kidney dysfunction, inflammatory conditions, various pains, or the like in human beings or animals.

Hitherto, such PGE_2 antagonist is known. For example, in WO 00/16760 and WO 00/18744, oxazole compounds are disclosed.

DISCLOSURE OF INVENTION

Under the above situation, the inventors of this invention found that the ornithine derivatives represented by the formula (I) and their salts are useful as PGE_2 agonists or antagonists, particularly EP4 receptor blockers. And the inventors completed this invention.

Accordingly, this invention relates to ornithine derivatives. More particularly, this invention relates to ornithine derivatives which are useful for treating or preventing PGE_2 mediated diseases.

That is, one object of this invention is to provide new and useful ornithine derivatives and pharmaceutically acceptable salts thereof.

Another object of this invention is to provide a pharmaceutical composition containing, as an active ingredient,

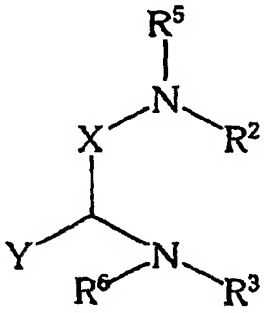
said ornithine derivatives or pharmaceutically acceptable salts thereof

A further object of this invention is to provide a use of the ornithine derivatives and pharmaceutically acceptable salts thereof for the manufacture of medicaments for treating or preventing PGE_2 mediated diseases.

A still further object of this invention is to provide a use of prostaglandin E_2 antagonist (especially, EP4 receptor blocker) such as ornithine derivatives and pharmaceutically acceptable salts thereof for the manufacture of medicaments for treating or preventing kidney function.

A still more further object of this invention is to provide a process for preparing the above ornithine derivatives and pharmaceutically acceptable salts thereof.

The ornithine derivatives of this invention can be represented by the following formula (I) :



(I)

wherein

Y is

(1) lower alkyl, or

(2) Z-(CH_2)n-,

{wherein

Z is

(1) aryl, or

(2) R^1-CO-NR^4-

(wherein
R^1 is (1) aryl, heterocyclic group, heterocyclic(lower)alkoxy, ar(lower)alkyl, or ar(lower)alkoxy, each of which may be substituted with one or more substituent(s) selected from the group consisting of
(a) halogen,
(b) hydroxy, and
(c) lower alkyl, or
(2) lower alkoxy, and
R^4 is hydrogen, or lower alkyl); and

n is an integer of 1, 2, 3, 4, 5 or 6};

R^2 is (1) ar(lower)alkyl, lower alkyl, or lower alkylthio(lower)alkyl, each of which may be substituted with one or more substituent(s) selected from the group consisting of
(a) carboxy,
(b) carboxy(lower)alkyl,
(c) amidated carboxy,
(d) esterified carboxy, and
(e) heterocyclic group,

or
(2) aryl which may be substituted with aryl, lower alkyl, lower alkylamino, lower alkoxy(lower)alkyl, lower alkylthio(lower)alkyl, lower alkylamino-(lower)alkyl, lower alkoxy, lower alkenyl, or lower alkylthio, each of which may be further substituted with one or more substituent(s) selected from the group consisting of
(a) carboxy,
(b) amidated carboxy,
(c) esterified carboxy, and

(d) heterocyclic group;

R^3 is (1) Q-R^7,

[wherein

Q is -CO- or -SO_2-,

R^7 is (a) heterocyclic group which may be substituted with

lower alkyl(s),

aryl(s) which may be substituted with halogen(s), or

halogen(s),

(b) cyclo(C_3-C_8)alkyl,

(c) aryl which may be substituted with

lower alkyl(s),

aryl(s),

halogen(s),

lower alkoxy(s),

aryloxy(s), or

hydroxy(s),

(d) lower alkyl which may be substituted with

cyclo(C_3-C_8)alkyl(s),

aryl(s) which may be substituted with

aryl(s), or

heterocyclic group(s),

(e) lower alkenyl which may be substituted with

aryl(s), or

heterocyclic group(s),

(f) amino which may be substituted with

aryl(s) which may be substituted with

aryl(s), or

heterocyclic group(s),

or

(g) aryloxy(s)],

or

(2) lower alkyl which may be substituted with

aryl(s) which may be substituted with aryl(s), or heterocyclic group(s);

R^5 and R^6 are independently hydrogen or lower alkyl; or

R^6 and Y may be linked together to form $-(CH_2)m-$, wherein m is an integer of 2, 3, 4 or 5; and

X is $-CO-$, or $-(CH_2)k-$;
wherein k is an integer of 1, 2 or 3,

or a pharmaceutically acceptable salt thereof.

The compounds of the formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. Furthermore certain compounds of the formula (I) which contain alkenyl groups may exist as cis- or trans-isomers. In each instance, the invention includes both mixtures and separate individual isomers.

The compounds of the formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

The compounds of the formula (I) and their salts can be in a form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

Also included in the scope of the invention are radiolabelled derivatives of the compounds of the formula (I), which are suitable for biological studies, and any form of the crystal of the compound (I).

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention includes within the scope thereof are explained in detail as follows.

Suitable "aryl" and aryl moiety in the terms "ar(lower)alkyl", and "aryloxy" may include phenyl, lower alkylphenyl (e.g., tolyl, ethylphenyl, propylphenyl, etc.), naphthyl or the like.

Suitable "halogen" may include fluorine, chlorine, bromine, or iodine.

The term "lower" is intended to mean 1 to 6 carbon atom(s), unless otherwise indicated.

Suitable "lower alkyl" and lower alkyl moiety in the terms "ar(lower)alkyl", "carboxy(lower)alkyl", "lower alkylthio(lower)alkyl", "lower alkylthio", "lower alkylamino", "lower alkoxy(lower)alkyl", and "lower alkylthio(lower)alkyl", "lower alkylamino(lower)alkyl" may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, t-pentyl, hexyl or the like, preferably one having 1 to 4 carbon atom(s).

Suitable "lower alkoxy" and lower alkoxy moiety in the term "heterocyclic(lower)alkoxy", "ar (lower)alkoxy", and "lower alkoxy(lower)alkyl" may include methoxy, ethoxy propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, t-pentyloxy, hexyloxy, or the like, preferably methoxy.

Suitable "lower alkenyl" may include straight or branched one having 1 to 6 carbon atom(s), such as methylenyl, ethylenyl, trimethylenyl, tetramethylenyl pentamethylenyl, and hexamethylenyl or the like, preferably one having 1 to 4 carbon atom(s).

Suitable "heterocyclic group" may include saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one hetero atom selected from nitrogen, sulfur and oxygen atom. And especially preferable heterocyclic group may be ones such as

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl,

pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, pyrimidinyl, pyrazinyl, dihydropyridazinyl, tetrahydropyridazinyl, triazolyl (e.g., 1H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), dihydrotriazinyl (e.g., 4,5-dihydro-1,2,4-triazinyl, 2,5-dihydro-1,2,4-triazinyl, etc.), etc.;

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, azacycloheptyl, azacyclooctyl, perhydroazepinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atom(s), for example, indolyl, 2,3-dihydroindolyl, isoindolyl, indolinyl, indazolyl, isoindolinyl, indolizinyl, benzimidazolyl, quinolyl, 1,2,3,4-tetrahydroquinolyl, isoquinolyl, benzotriazolyl, tetrazolopyridyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl,etc.), dihydrotriazolopyridazinyl, quinoxalinyl, etc.;

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 oxygen atom(s), for example, furyl, pyranyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 4 oxygne atom(s), for example, beozofuryl, chromenyl, etc.;

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, dihydroisoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 2,5-oxadiazolyl, etc.), etc.;

saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholino, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated 3 to 8-membered heteromonocyclic group

containing 1 to 2 sulfur atom(s), for example, thienyl, thiepinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, naphto[2,3-b]thienyl, thianthrenyl, etc.;

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiazolinyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-thiadiazolyl), etc.;

unsaturated condensed heterocyclic group containing 1 to 5 sulfur atom(s), for example, benzothienyl, benzothieteyl, etc.;

saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;

unsaturated condensed heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc. and the like.

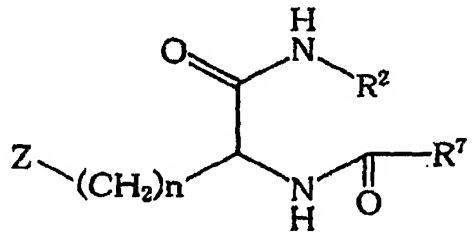
Suitable "cyclo(C_3-C_8)alkyl" may include cyclopropyl, cyclopentyl, cyclobutyl, cyclohexyl, cycloheptyl, cyclooctyl, or the like.

Suitable example of the ester moiety in the term "esterified carboxy" may be the ones such as lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, etc.) which may have at least one suitable substituent(s), for example, lower alkanoyloxy(lower)alkyl [e.g., acetoxymethyl, butyryloxymethyl, valeryloxymethyl, pivaloyloxymethyl, etc.], halo(lower)alkyl (e.g., 2-iodoethyl, 2,2,2-trichloroethyl, etc.); lower alkenyl (e.g., vinyl, allyl, etc.); lower alkynyl (e.g., ethynyl, propynyl, etc.); ar(lower)alkyl which may have at least one suitable substituent(s) (e.g., benzyl, 4-methoxybenzyl, 4-nitrobenzyl, phenethyl, trityl, etc.); aryl which may have at least one

suitable substituent(s) (e.g., phenyl, tolyl, 4-chlorophenyl, tert-butylphenyl, xylyl, mesityl, cumenyl, etc.); phthalidyl; or the like.

Suitable "amidated carboxy" may include carbamoyl which may be substituted with ar(lower)alkyl(s) (e.g., benzyl, phenylethyl, phenylpropyl, etc.), or the like.

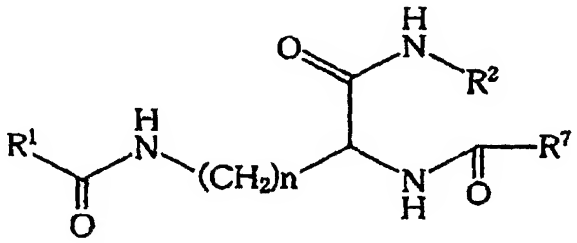
Preferred embodiments of the compounds (Ia) are as follows:



(Ia)

wherein R^2, R^7, n and Z are each as defined above.

More preferred embodiments of the compounds (Ib) are as follows :



(Ib)

wherein R^1, R^2, R^7 and n are each as defined above.

The most preferred embodiment of the ornithine derivatives (I) is.

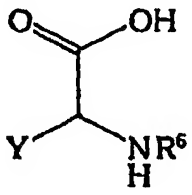
R^1 is ar(lower)alkoxy;

n is an integer of 1, 2, 3, 4 or 5;

R^2 is lower alky, or
aryl which may be substituted with carboxy-(lower)alkyl;
R^7 is heterocyclic group which may be substituted with lower alkyl.

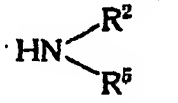
The processes for preparing the object compound (I) of the present invention, especially the typical compounds (Ia) and (Ib) are explained in the following processes 1-1 to 2.

Process1-1

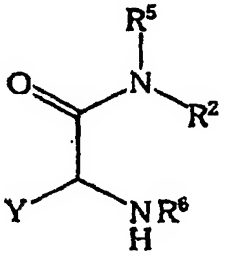


(IIa)
or its reactive derivative at carboxy grunp, or the salt thereof

step a

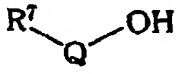


(IIIa)
or its reactive derivative at amino grunp, or the salt thereof

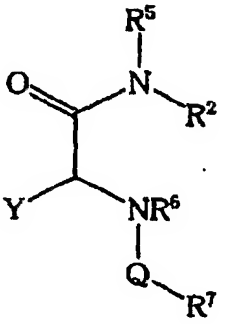


(IVa)
or its salt

step b

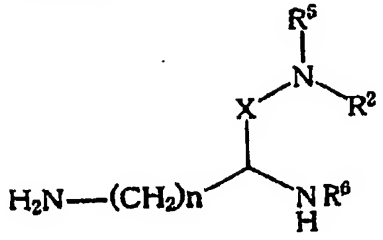


(V)
or its reactive derivative at carboxy grunp, or the salt thereof



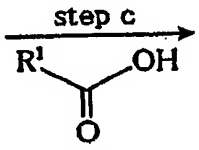
(Ia-1)
or its salt

Process1-2

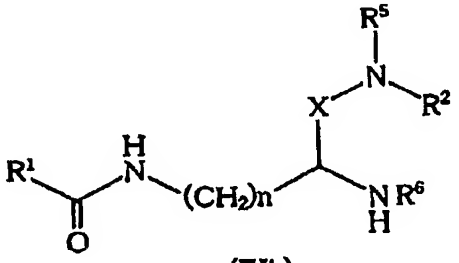


(IIb)
or its reactive derivative at amino grunp, or the salt thereof

step c

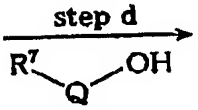


(IIIb)
or its reactive derivative at carboxy grunp, or the salt thereof

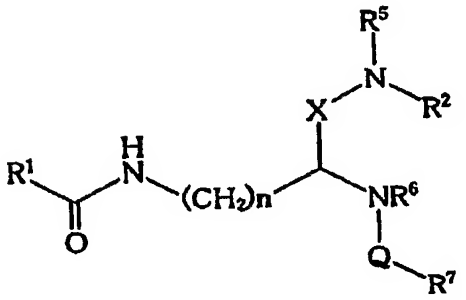


(IVb)
or its salt

step d

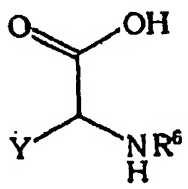


(V)
or its reactive derivative at carboxy grunp, or the salt thereof



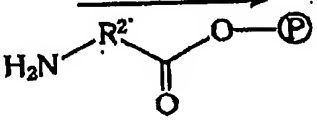
(Ib-1)
or its salt

Process2

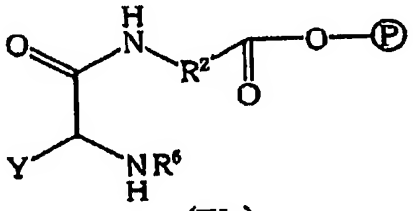


(IIa)
or its reactive
derivative at
carboxy grunp,
or the salt thereof

step f

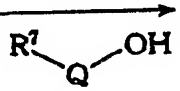


(IIIc)
or its reactive
derivative at
amino grunp,
or the salt thereof

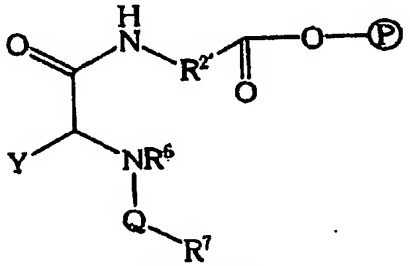


(IVc)
or its salt

step g



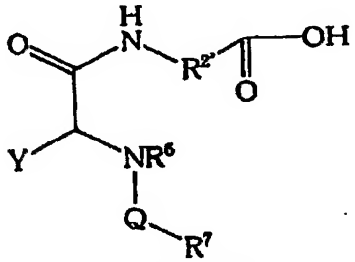
(V)
or its reactive
derivative at
carboxy grunp,
or the salt thereof



(I a-2')
or its salt

step h

cleavage of Ⓟ



(I a-2)
or its salt

{wherein
R^1, R^2, R^3, R^4, R^5, R^6, R^7, Q, X, Y, Z and n are each as defined above;
$R^{2'}$ is
(1) ar(lower)alkyl, lower alkyl,
lower alkylthio(lower)alkyl, or
(2) aryl which may be substituted with

aryl, lower alkyl, lower alkylamino,
lower alkoxy(lower)alkyl,
lower alkylthio(lower)alkyl,
lower alkylamino(lower)alkyl, lower alkoxy,
lower alkenyl, or lower alkylthio; and

Ⓟ is polymer.}

Process 1-1

The compound (Ia-1) or its salt can be prepared by the following steps:

(i) reacting the compound (IIa) or its reactive derivative at the carboxy group, or the salt thereof, with the compound (IIIa) or its reactive derivative at the amino group, or the salt thereof to give the compound (IVa) or its salt [step a]; and

(ii) reacting the obtained compound (IVa) or its salt, with the compound (V) or its reactive derivative at the carboxy group (in case of Q is -CO-)/the sulfo group (in case of Q is $-SO_2-$), or the salt thereof [step b].

The above Process 1-1 comprises:

(i) preparing the intermediate compound (IVa) from the carboxylic acid compound (IIa) and the amine compound (IIIa) in solvent; and

(ii) preparing the desired compound (Ia-1) from the the intermediate amine compound (IVa) and the carboxylic acid compound (V) in case of Q is -CO-/sulfonic acid compound (V) in case of Q is $-SO_2-$.

[step a] in Process 1-1

In this process, the amine compoud (IIIa) can be used on sale or can be synthesized according to general methods obvious to the person skilled in the organic chemistry from commercial compounds.

Suitable reactive derivative of the amine compoud (IIIa) may include Schiff's base type imino or its tautomeric enamine

type isomer formed by the reaction of the compound (IIIa) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (IIIa) with a silylating reagent such as N,O-bis(trimethylsilyl)-acetamide, N-trimethylsilylacetamide,or the like.

Suitable reactive derivative of the carboxylic acid compound (IIa) may include an acid halide (carbonyl chloride, carbonyl bromide, etc.), an acid anhydride, an acid activated amide, an activated ester, or the like.

Suitable acid anhydride may be a symmetric anhydride or a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfuric acid, thiosulfuric acid, alkanesulfonic acid (e.g., methanesulfonic acid, ethanesulfonic acid, etc.), alkylcarbonic acid, aliphatic carboxylic acid (e.g., pivalic acid, pentanoic acid, isopentanoic acid, etc.); aromatic carboxylic acid (e.g., benzoic acid, chlorobenzoic acid, fluorobenzoic acid, nitrobenzoic acid, etc.), or the like.

Suitable activated amide may be imidazolylamide, 4-substituted imidazolylamide, dimethylpyrazolylamide, triazolylamide, tetrazolylamide, or the like.

Suitable activated ester may be dimethyliminomethyl [$(CH_3)_2N^+=CH-$] ester, vinyl ester, propargyl ester, 4-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, pentafluorophenyl ester, methanesulfonylphenyl ester, phenyl thioester, p-nitrophenyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, 8-quinolyl thioester, an activated ester with a N-hydroxy compound (e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2H-pyridone, N-hydroxysuccinimide, N-hydroxybenzotrioxazole, N-hydroxyphthalimide, etc.), or the like.

When the carboxylic acid compound (IIa) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of condensing agent.

Suitable condensing agent may include a carbodiimide [e.g., N,N'-diisopropylcarbodiimide (DIPCI), N,N'-dicyclohexylcarbodiimide (DCC), N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide or its hydrochloride], diphenylphosphinic azido, diphenylphosphinic chloride, diethylphosphoryl cyanide, bis(2-oxo-3-oxazolidinyl)phosphinic chloride, N,N'-carbonyldiimidoxazole, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, cyanuric chloride, or the like.

The reaction may be also carried out in the presence of organic or inorganic base such as alkali metal carbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorphorine, or the like.

The reaction is usually carried out in a conventional solvent such as water, acetone, alcohol [e.g., methanol, ethanol, isopropyl alcohol, etc.], THF, dioxane, toluene, methylene chloride, chloroform, DMF or any other organic solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

For example, this reaction can be referred to that of Example 27-1.

[step b] in Process 1-1

(i) in the case of Q is -CO-

Suitable reactive derivative of the carboxy compound (V), the condensing agent, base, solvent employable in this process and the reaction temperature are the same as explained above.

This reaction can be referred to that of Example 27-3.

(ii) in the case of Q is $-SO_2-$

Suitable reagent to be used in the sulfonylation is, for example, sulfonyl chloride, sulfonic anhydride (e.g., trifluoromethanesulfonic anhydride, etc.) or the like. This reaction is preferably carried out in the presence of base.

Suitable base may include the inorganic base such as alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), alkaline earth metal hydroxide (e.g., magnesium hydroxide, calcium hydroxide, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), alkaline earth metal carbonate (e.g., magnesium carbonate calcium carbonate, etc.) or the like; and the organic base such as tri(lower)alkylamine {e.g., trimethylamine, diisopropylethylamine (DIPEA), etc.}, pyridine, or the like.

This reaction is usually carried out in a conventional solvent such as toluene, acetonitrile, benzene, DMF, THF,, methylene chloride, ethylene chloride, chloroform, or any other organic solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

In the above processes, all compounds may be timely introduced by protective group or deprotected at active position. Therefore, the carboxy group and the amino group may be protected and the protective group thereof may be cleaved on cue. Concerning the kind of protective group and the reactive condition of the formation and cleavage, 「PROTECTIVE GROUPS IN ORGANIC SYNTHESIS Second Edition」 T.W.Green and P.G.M.Wuts, John Wiley & Sons, INC. may be referred. For example, the method employed in the reaction relies on masking the secondary amine in the compound as an N-Boc (N-tert-butoxycarbonyl) derivative, Fmoc (9-fluorenylmethoxycarbonyl) derivative, or the like.

In some cases, the compound (Ia-1) from the reaction

described above may be further modified, for example by the manipulation substituents. The manipulations may be included, but are not limited to reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art.

Process 1-2

The compound (Ib-1) or its salt can be prepared by the following steps:

(i) reacting the compound (IIb) or its reactive derivative at the amino group, or the salt thereof, with the compound (IIIb) or its reactive derivative at the carboxy group, or the salt thereof to give the compound (IVb) or its salt [step c]; and

(ii) reacting the compound (IVb) or its salt, with the compound (V) or its reactive derivative at the carboxy group (in case of Q is -CO-)/the sulfo group (in case of Q is $-SO_2-$), or the salt thereof [step d].

The above Process 1-2 comprises:

(i) preparing the intermediate compound (IVb) from the amine compound (IIb) and the carboxylic acid compound (IIIb) in solvent; and

(ii) preparing the desired compound (Ib-1) from the obtained amine compound (IVb) and the carboxylic acid compound (V) in case of Q is -CO-/sulfonic acid compound (V) in case of Q is $-SO_2-$.

[step c] in Process 1-2

In this process, the compound (IIb) can be obtained in a similar manner to that of [step b] in Process 1-1.

This reaction can be referred to that of Example 36-2.

[step d] in Process 1-2

In this process, the compound (Ib-1) can be obtained in a similar manner to that of [step b] in Process 1-1.

This reaction can be referred to that of Example 27-3.

In the above processes, all compounds may be timely introduced by protective group or deprotected at active position. Therefore, the carboxy group and the amino group may be protected and the protective group thereof may be cleaved on cue. Concerning the kind of protective group and the reactive condition of the formation and cleavage, 「PROTECTIVE GROUPS IN ORGANIC SYNTHESIS Second Edition」 T.W.Green and P.G.M.Wuts, John Wiley & Sons, INC. may be referred. For example, the method employed in the reaction relies on masking the secondary amine in the compound as an N-Boc (N-tert-butoxycarbonyl) derivative, Fmoc (9-fluorenylmethoxycarbonyl) derivative, or the like.

In some cases, the compound (Ib-1) from the reaction described above may be further modified, for example by the manipulation substituents. The manipulations may be include, but are not limited to reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art.

Process 2

In addition, the compound (I) may be obtained on a solid phase support linkage illustrated above.

For example, the compound (Ia-2) or its salt can be prepared by the following steps:

(i) preparing the resin-bound amine compound (IIIc) [step e];

(ii) reacting the carboxylic acid compound (IIa) or its reactive derivative at the carboxy group, or the salt thereof, with the above resin-bound amine compound (IIIc) or its reactive derivative at the amino group, or the salt thereof to give the amine compound (IVc) or its salt [step f];

(iii) reacting the amine compound (IVc) or its salt, with the compound (V) or its reactive derivative at the carboxy group (in case of Q is -CO-)/the sulfo group (in case of Q is $-SO_2-$), or the salt thereof [step g]; and

(iv) a cleavage reaction of the resin [step h].

[step e] in Process 2

The resin-bound amine compound (IIIc) is coupled to a solid support such as trytyl-resin by treatment with an activating agent, conveniently 4-nitrophenyl chloroformate in the presence of base such as DIPEA in a solvent such as THF, DMF, dichloromethane, or their mixture.

This reaction can be referred to that of Example 1.

[step f] and [step g] in Process 2

In these processes, the compounds (IVc) and (Ia-2) can be obtained in a similar manner to that of [step b] in Process 1-1.

This reaction can be referred to that of Examples 1 and 27-3.

[step h] in Process 2

Cleavage from the resin is effected, in the case of trytyl resin, by treatment with acid such as trifluoroacetic acid (TFA) as mixture with dichloromethane, or the like.

This reaction can be referred to that of Example 1.

In the above processes, all compounds may be timely introduced by protective group or deprotected at active position. Therefore, the carboxy group and the amino group may be protected and the protective group thereof may be cleaved on cuc. Concerning the kind of protective group and the reactive condition of the formation and cleavage, 「PROTECTIVE GROUPS IN ORGANIC SYNTHESIS Second Edition」 T.W.Green and P.G.M.Wuts, John Wiley & Sons, INC.

may be referred. For example, the method employed in the reaction relies on masking the secondary amine in the compound as an N-Boc (N-tert-butoxycarbonyl) derivative, Fmoc (9-fluorenylmethoxycarbonyl) derivative, or the like.

In some cases, the compound (Ia-2) from the reaction described above may be further modified, for example by the manipulation substituents. The manipulations may be included, but are not limited to reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art.

Suitable salts of the object compound (I) including the compounds (Ia-1), (Ia-2), and (Ib) are pharmaceutically acceptable conventional non-toxic salts and include a metal salt such as an alkali metal salt (e.g., sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, etc.), an organic acid salt (e.g., acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.), or the like.

These compounds can be converted to their salts according to a conventional method.

As described above, the ornithine derivatives of the present invention are useful for treating or preventing kidney dysfunction (acute nephritic syndrome, recurrent or persistent hematuria, chronic nephritic syndrome, nephritic syndrome, rapidly progressive nephritic syndrome, acute renal failure, chronic renal failure, etc.), inflammation and pain in joint and muscle (e.g., rheumatoid arthritis, rheumatoid

spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, etc.), inflammatory skin condition (e.g., sunburn, burns, eczema, dermatitis, etc.), inflammatory eye condition (e.g., conjunctivitis, etc.), lung disorder in which inflammation is involved (e.g., asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.), condition of the gastrointestinal tract associated with inflammation (e.g., aphthous ulcer, Chrohn's disease, atrophic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.), gingivitis, inflammation, nephrithis, pain and tumescence after operation or injury, pyrexia, pain and other conditions associated with inflammation, allergic disease, systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodose, rheumatic fever, Sjgren's syndrome, Behcet disease, thyroiditis, type I diabetes, diabetic complication (diabetic microangiopathy, diabetic retinopathy, diabetic nephropathy, etc.), nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis, contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimers disease, migraine, liver dysfunction (hepatitis, cirrhosis, etc.), gastrointestinal dysfunction (diarrhea, inflammatory bowel diseases, etc.), shock, bone disease characterized by abnormal bone metabolism such as osteoporosis (especially, postmenopausal osteoporosis), hyper-calcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodontitis, osteoarthritis, ostealgia, osteopenia cancer, cancer cachexia, breast cancer, calculosis, lithiasis (especially, urolithiasis), solid caricinoma, neurodegenerative disorder, sleeping disorder, hyperaldosteronism sexual dysfunction, or the like in human being or animal.

The compound represented by the formula (I) or its salts are also useful for the preparation of medicament having diuretic activity, which are useful for the preparation of drugs

indicated treating or preventing various edema (e.g. cardiac edema, cerebral edema, etc.), hypertension such as malignant hypertension or the like, premenstrual tension, urinary calculus, oliguria such as the one caused by acute or chronic failure, hyperphosphaturia, or the like.

In order to show the utility of the object compound (I), pharmacological data of the representative compounds thereof are shown in the following.

Binding assay using membrane preparation with the expression of prostanoid receptor subtype

[I] Test Compound:

sodium 6-{(2S)-2-[(1-benzofuran-2-yl-carbonyl)-amino]-5-[benzyloxycarbonylamino]pentanoylamino}-hexanoate (Example 23)

[II] Test Method:

The membrane fraction was prepared using COS-7 cells transfected prostanoid receptor subtype (human EP4).

The standard assay mixture contained membrane fraction, [^{3}H]-PGE_2 in final volume of 0.25ml was incubated for 1hr at 30℃. The reaction was terminated by that the mixture was rapidly filtered through a glass filter (GF/B). Then the filter was washed with 4ml of ice-cooled buffer two times. The radioactivity associated with the filter was measured by liquid scintillation counting.

In the experiment for competition of specific [^{3}H]-PGE_2 was added at a concentration of 10nM. The following buffer was used in all reactions.

Buffer: 20mM Mes (pH 6.0), 1mM EDTA, 10mM $MgCl_2$

The inhibition (%) of the compound at a concentration of 10nM was shown below.

[III] Test Result:

The test compound (1.0×10^{-8}M) showed the inhibition of 80% or more.

The pharmaceutical composition of the present invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form (e.g., tablet, pellet, troche, capsule, suppository, cream, ointment, aerosol, powder, solution, emulsion, suspension etc.), which contains the object compound (I) or a pharmaceutically acceptable salt thereof as an active ingredient, suitable for rectal, pulmonary (nasal or buccal inhalation), nasal, ocular, external (topical), oral or parenteral (including subcutaneous, intravenous and intramuscular) administrations or insufflation.

The pharmaceutical composition of this invention can contain various organic or inorganic carrier materials, which are conventionally used for pharmaceutical purpose, such as excipient (e.g., sucrose, starch, mannit, sorbit, lactose, glucose, cellulose, talc, calcium phosphate, calcium carbonate, etc.), binding agent (e.g., cellulose, methyl cellulose, hydroxypropylcellulose, polypropylpyrrolidone, gelatin, gum arabic, polyethyleneglycol, sucrose, starch, etc.), disintegrator (e.g., starch, carboxymethyl cellulose, calcium salt of carboxymethyl cellulose, hydroxypropylstarch, sodium glycol-starch, sodium bicarbonate, calcium phosphate, calcium citrate, etc.), lubricant (e.g., magnesium stearate, talc, sodium laurylsulfate, etc.), flavoring agent (e.g., citric acid, mentol, glycine, orange powders, etc.), preservative (e.g., sodium benzoate, sodium bisulfite, methylparaben, propylparaben, etc.), stabilizer (e.g., citric acid, sodium citrate, acetic acid, etc.), suspending agent (e.g., methyl cellulose, polyvinylpyrrolidone, aluminum stearate, etc.), dispersing agent, aqueous diluting agent (e.g., water), base wax (e.g., cacao butter, polyethylene-glycol, white petrolatum, etc.).

The effective ingredient may usually be administered

with a unit dose of 0.01mg/kg to 50mg/kg, 1 to 4 times a day. However, the above dosage may be increased or decreased according to age, weight, conditions of the patient or the administering method.

The patents, patent applications and publications cited herein are incorporated by reference.

Abbreviations used in this application are as follows:

EtOAc	ethyl acetate
DMF	N,N-dimethylformamide
Boc	tert-butoxycarbonyl
Fmoc	9-fluorenylmethoxycarbonyl
WSCD	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide
DIPCI	1,3-diisopropylcarbodiimide
TBTU	o-benzotriazole-N,N,N,N'-tetramethyl-uronium-hexafluorophosphate
HOBT	1-hydroxybenzotriazole
THF	tetrahydrofuran
NaOH	sodium hydroxide
DIPEA	N,N-diisopropylethylamine
EtOH	ethanol
MeOH	methanol
$MgSO_4$	magnesium sulfate
HCl	hydrochloric acid

The following Preparations and Examples are given only for the purpose of illustrating the present invention in more detail.

Example 1

A solution of 6-[9-(flouorenylmethoxycarbonyl)amino]-hexanoic acid (180mg) and DIPEA (0.12mL) in dichloromethane (3mL) was added to a reaction vessel containing Cl-trytyl resin

(200mg, 1.3mmol/g, loading). After the vessel was shaken for 12hrs at an ambient temperature, the resin was washed successively with dichloromethane, THF, DMF, and dichloromethane.

After cleavage 9-(flouorenylmethoxycarbonyl)amide using 20% piperazine in DMF (5mL),2-[9-(flouorenylmethoxy-carbonyl)amino]-5-[benzyloxycarbonylamino]pentanoic acid (254mg), TBTU (170mg), HOBT (70mg) and DIPEA (0.18mL) was added to a solution of the obtained resine in DMF (3mL). After the vessel was shaken for 12hrs at an ambient temperature, the resin was washed successively with dichloromethane, THF, DMF, and dichloromethane.

After cleavage 9-(flouorenylmethoxycarbonyl)amide using 20% piperazine in DMF (5mL), benzofuran-2-carboxylic acid (210mg), DIPCI (0.21mL) and DIPEA (0.23mL) was added successively to a solution of the obtained resine in dichloromethane (3mL). After the vessel was shaken for 12hrs at an ambient temperature, the resin was washed successively with dichloromethane, THF, DMF, and dichloromethane.

Cleavage from the resin was performed with 1% trifluoromethanesulfonic acid in dichloromethane (5mL) for 10min at an ambient temperature. After the filtrated solvent was evaporated under pressure, the residue was washed with ether to give 6-{(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino}hexanoic acid (100mg, 72%).

Ms: 524(M+1)

Example 2

The following compound was obtained in a similar manner to that of Example 1.

{(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[benzyl-oxycarbonylamino]pentanoylamino}acetic acid

Ms: 468(M+1)

Example 3

The following compound was obtained in a similar manner to that of Example 1.

4-{(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[benzyl oxycarbonylamino]pentanoylamino}butanoic acid

Ms: 496(M+1)

Example 4

The following compound was obtained in a similar manner to that of Example 1.

5-{(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[benzyl oxycarbonylamino]pentanoylamino}pentanoic acid

Ms: 510(M+1)

Example 5

The following compound was obtained in a similar manner to that of Example 1.

7-{(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[benzyl oxycarbonylamino]pentanoylamino}heptanoic acid

Ms: 538(M+1)

Example 6

The following compound was obtained in a similar

manner to that of Example 1.

6-{(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-3-[benzyl oxycarbonylamino]propanoylamino}hexanoic acid

Ms: 496(M+1)

Example 7

The following compound was obtained in a similar manner to that of Example 1.

6-{(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-4-[benzyl oxycarbonylamino]butanoylamino}hexanoic acid

Ms: 510(M+1)

Example 8

The following compound was obtained in a similar manner to that of Example 1.

6-{(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-6-[benzyl oxycarbonylamino]hexanoylamino}hexanoic acid

Ms: 538(M+1)

Example 9

The following compound was obtained in a similar manner to that of Example 1.

6-{(2R)-2-[(1-benzofuran-2-ylcarbonyl)amino]-6-[benzyl oxycarbonylamino]hexanoylamino}hexanoic acid

Ms: 538(M+1)

Example 10

The following compound was obtained in a similar manner to that of Example 1.

6-{(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-3-phenylpropanoylamino}hexanoic acid

Ms: 423(M+1)

Example 11

The following compound was obtained in a similar manner to that of Example 1.

6-{(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-3-methylbutanoylamino}hexanoic acid

Ms: 375(M+1)

Example 12

The following compound was obtained in a similar manner to that of Example 1.

6-[(2S)-1-(1-benzofuran-2-ylcarbonyl)-2-(pyrrolidinyl)-carbonylamino]hexanoic acid

Ms: 373(M+1)

Example 13

The following compound was obtained in a similar manner to that of Example 1.

6-{(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[ethoxy carbonylamino]pentanoylamino}hexanoic acid

Ms: 476(M+1)

Example 14

The following compound was obtained in a similar manner to that of Example 1.

6-{(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[benzoylamino]pentanoylamino}hexanoic acid

Ms: 494(M+1)

Example 15

The following compound was obtained in a similar manner to that of Example 1.

6-{(2S)-2,5-bis[(1-benzofuran-2-ylcarbonyl)amino]-pentanoylamino}hexanoic acid

Ms: 534(M+1)

Example 16

The following compound was obtained in a similar manner to that of Example 1.

6-{(2S)-2-[(1-benzothien-2-ylcarbonyl)amino]-5-[benzyl oxycarbonylamino]pentanoylamino}hexanoic acid

Ms: 540(M+1)

Example 17

The following compound was obtained in a similar manner to that of Example 1.

6-{(2S)-2-[(2E)-(3-phenyl-2-propenoyl)amino]-5-[benzyl oxycarbonylamino]pentanoylamino}hexanoic acid

Ms: 510(M+1)

Example 18

The following compound was obtained in a similar manner to that of Example 1.

6-{(2S)-2-[(4-biphenylylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino}hexanoic acid

Ms: 560(M+1)

Example 19

The following compound was obtained in a similar manner to that of Example 1.

6-{(2S)-2-[(2-naphthoyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino}hexanoic acid

Ms: 534(M+1)

Example 20

The following compound was obtained in a similar manner to that of Example 1.

6-{(2S)-2-[(1H-indol-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino}hexanoic acid

Ms: 523(M+1)

Example 21

The following compound was obtained in a similar manner to that of Example 1.

6-{(2S)-2-[(3a,7a-dihydro-1H-indol-3-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino}hexanoic acid

Ms: 523(M+1)

Example 22

The following compound was obtained in a similar manner to that of Example 1.

6-{(2S)-2-[(1H-indol-6-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino}hexanoic acid

Ms: 523(M+1)

Example 23

To a solution of 6-{(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino}hexanoic acid (50mg) obtained by Example 1 in MeOH was added 1N NaOH (0.1mL) at an ambient temperature. After the solvent was evaporated under pressure, the residue was washed with ether to give sodium 6-{(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino}hexanoate (50mg).

Ms: 524(M+1)

NMR(200MHz, DMSO-d_6): 1.2-1.8(10H, m), 1.95(2H, t, J=7.0Hz), 3.03(4H, t, J=6.2Hz), 4.43(1H, m), 4.99(2H s), 7.2-7.6(8H, m), 7.6-7.9(3H, m), 8.31(1H, t, J=5.4Hz), 8.87(1H d, J=8.2Hz)

Example 24

To a solution of 6-{(2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-[benzyloxycarbonylamino]pentanoylamino}hexanoic acid (50mg) obtained by Example 1 in DMF (1mL) were added successively TBTU (84mg) and HOBT (18mg) and DIPEA (0.023mL), and benzylamine (0.014mL) at an ambient temperature. After stirring for 4hrs, the mixture was diluted

with EtOAc. The solution was washed successively with water, 1N HCl, 1N NaOH, and brine, and dried over $MgSO_4$. After the filtrated solvent was evaporated under pressure, the residue was washed with ether to give benzyl N-{(4S)-4-[(1-benzofuran-2-yl-carbonyl)amino]-5-oxo-5-[(6-oxo-6-benzylaminohexyl)amino]pentyl}carbamate (40mg).

Ms: 613(M+1)

Example 25

The following compound was obtained in a similar manner to that of Example 24.

benzyl N-{(4S)-4-[(1-benzofuran-2-ylcarbonyl)amino]-5-oxo-5-[6-oxo-6-[(2-phenylethylaminohexyl)amino]pentyl]-carbamate

Ms: 627(M+1)

Example 26

The following compound was obtained in a similar manner to that of Example 24.

benzyl N-{(4S)-4-[(1-benzofuran-2-ylcarbonyl)amino]-5-oxo-5-[6-oxo-6-[(3-phenylpropylaminohexyl)amino]pentyl]-carbamate

Ms: 641(M+1)

Example 27-1

To a solution of (2S)-2-[tert-butoxycarbonylamino]-5-[benzyloxycarbonylamino]pentanoic acid (6.00g) and methyl (2E)-3-(2-aminophenyl)acrylate (3.77g) in DMF (60mL) were added successively HOBT (3.32g), WSCD hydrochloride (6.28g), and 4-(dimethylamino)pyridine (400mg). The mixture was

stirred at 50℃ for 15hrs. After cooling to room temperature, the mixture was quenched by the addition of water (120mL) and extracted with EtOAc (120mL). The extract was washed successively with water (120mL), saturated aqueous sodium hydrogencarbonate (120mL), 1N HCl (120mL), water (120mL), and brine (120mL), and dried over $MgSO_4$. Filtration followed by evaporation gave a crude product which was chromatographed on silica gel (eluent:hexane/EtOAc=1/1) to give methyl (2E)-3-{2-[(2S)-5-[benzyloxycarbonylamino]-2-[tert-butoxycarbonylamino]pentanoylamino]phenyl}acrylate (2.58g) as a yellow crystalline solid.

(+)ESI-MS(m/z) : 548$(M+Na)^+$

Example 27-2

To a suspension of methyl (2E)-3-{2-[(2S)-2-[tert-butoxycarbonylamino]-5-[benzyloxycarbonylamino]pentanoylamino]-phenyl}acrylate (2.58g) in EtOAc (20mL) was added 4N hydrogen chloride in EtOAc (20mL) and the mixture was stirred at room temperature for 1hr. The solvent was removed by evaporation to give methyl (2E)-3-{2-[(2S)-2-amino-5-[benzyloxycarbonylamino]pentanoylamino]phenyl}acrylate hydrochloride (2.40g) as a yellow solid.

(+)ESI-MS(m/z) : 426$(M+H)^+$, 448$(M+Na)^+$

Example 27-3

To a solution of methyl (2E)-3-{2-[(2S)-2-amino-5-[benzyloxycarbonylamino]pentanoylamino]phenyl}acrylate hydrochloride (400mg) in DMF (4.0mL) were added successively indole-2-carboxylic acid (154mg), HOBT (176mg), and WSCD (0.32mL) and the mixture was stirred at room temperature for 16hrs. The mixture was diluted with EtOAc (10mL) and washed with water (10mL×2). The organic layer was stirred vigorously at room temperature for 1hr. The

precipitates were collected by filtration, washed with EtOAc (1mL×2), and dried under reduced pressure to give methyl (2E)-3-{2-[(2S)-2-[(1H-indol-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino]phenyl}acrylate (115mg) as a white solid.

(+)ESI-MS(m/z) : 591$(M+Na)^+$

Example 28

To a suspension of methyl (2E)-3-{2-[(2S)-2-[(1H-indol-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino]phenyl}acrylate (109mg) in MeOH (2.0mL) and THF (2.0mL) was added 1N NaOH (0.38mL)and the mixture was refluxed for 2 hrs. After cooling to room temperature, the mixture was quenched by the addition of 1N HCl (20mL) and extracted with EtOAc (20mL). The extract was washed with water (20mL) and brine (20mL), and dried over $MgSO_4$. Filtration followed by evaporation gave (2E)-3-{2-[(2S)-2-[(1H-indol-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]-pentanoylamino]phenyl}acrylic acid (102mg) as a pale yellow solid.

(-)ESI-MS (m/z): 553 $(M-H)^-$

^{1}H NMR (200MHz, DMSO-d_6, δ) : 1.61-1.99(4H, m), 3.05-3.11(2H, m), 4.63-4.79(1H, m), 5.01(2H, s), 6.49(1H, d, J=15.9Hz), 7.00-7.83(16H, m), 8.61(1H, d, J=7.7Hz), 10.0(1H, brs), 11.6(1H, brs),12.9(1H, brs)

Example 29

The following compound was obtained in a similar manner to that of Example 27-3.

methyl (2E)-3-{2-[(2S)-2-[(1-methyl-1H-indol-2-yl-carbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino]-phenyl}acrylate

(+)ESI-MS(m/z) : 605$(M+Na)^+$

Example 30

The following compound was obtained in a similar manner to that of Example 28.

(2E)-3-{2-[(2S)-2-[(1-methyl-1H-indol-2-ylcarbonyl)-amino]-5-[benzyloxycarbonylamino]pentanoylamino}phenyl}-acrylic acid

(-)ESI-MS (m/z) : 567 $(M-H)^-$

^{1}H NMR (200MHz, DMSO-d_6, δ) : 1.61-1.99(4H, m), 3.09-3.11(2H, m), 3.99(3H, s), 4.60-4.71(1H, m), 5.01(2H, s), 6.49(1H, d, J=15.9Hz), 7.07-7.84(16H, m), 8.62(1H, d, J=7.7Hz), 9.97(1H, brs), 12.4(1H, brs)

Example 31

The following compound was obtained in a similar manner to that of Example 27-3.

methyl (2E)-3-{2-[(2S)-2-[(4-biphenylylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino]phenyl}acrylate

(+)ESI-MS(m/z) :628$(M+Na)^+$

Example 32

The following compound was obtained in a similar manner to that of Example 28.

(2E)-3-{2-[(2S)-2-[(4-biphenylylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino]phenyl}acrylic acid

(-)ESI-MS (m/z) :590 $(M-H)^-$

^{1}H NMR (200MHz, DMSO-d_6, δ) : 1.60-1.99(4H, m),

3.08-3.11(2H, m), 4.64-4.79(1H, m), 5.01(2H,s), 6.48(1H, d, J=15.9Hz), 7.19-7.54(12H, m), 7.73-7.83(6H, m), 8.04(2H, d, J=8.4Hz), 8.66(1H, d, J=7.5Hz), 9.97(1H, brs), 12.4(1H, brs)

Example 33

The following compound was obtained in a similar manner to that of Example 27-3.

methyl (2E)-3-{2-[(2S)-2-[(1-benzofuran-2-ylcarbonyl)-amino]-5-[benzyloxycarbonylamino]pentanoylamino]phenyl}-acrylate

(+)ESI-MS(m/z) : 592$(M+Na)^+$

Example 34-1

To a solution of methyl (2E)-3-{2-[(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]-pentanoylamino]phenyl}acrylate (1.30g) in MeOH (26mL) and THF (26mL) was added 10% palladium on activated carbon (50% wet, 130mg) and the mixture was hydrogenated (1 atm) at room temperature for 90min. The catalyst was removed by filtration through a Celite cake and washed with MeOH. The filtrate was concentrated in vacuo to give methyl 3-{2-[(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[aminopentanoylamino]-phenyl}propanoate (1.19g) as a white solid.

Example 34-2

To a solution of methyl 3-{2-[(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-amino-pentanoylamino]phenyl}propanoate (1.05g) in THF (10mL) and water (10mL) was added benzyl chloroformate (0.38mL) at 5℃ while the pH was adjusted to 8.0-9.0 by the addition of 10% aqueous NaOH. After stirring at the same temperature for 30min, the mixture was extracted with EtOAc (20mL). The extract was washed with water (20mL) and brine (20mL), and dried over $MgSO_4$. Filtration

followed by evaporation gave a crude solid which was purified by silica gel chromatography (eluent:hexane/EtOAc=1/1) and recycling preparative HPLC equipped with a gel permeation chromatography column (eluent:chloroform) to give methyl 3-{2-[(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[benzyloxy carbonylamino]pentanoylamino]phenyl}propanoate (572mg) as a white crystalline solid.

(+)ESI-MS(m/z) : 594$(M+Na)^+$

Example 35

The following compound was obtained in a similar manner to that of Example 28.

3-{2-[(2S)-2-[(1-benzofuran-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino]phenyl}propanoic acid

(-)ESI-MS(m/z) : 556$(M-H)^-$

^{1}H NMR (200MHz, DMSO-d_6, δ) : 1.57-1.99(4H, m), 2.45-2.51(2H, m), 2.78-2.85(2H, m), 3.06-3.09(2H, m), 4.65-4.68(1H, m), 5.00(2H, s), 7.11-7.52(12H, m), 7.66-7.81(3H, m), 8.75(1H, d, J=7.7Hz), 9.62(1H, brs), 12.2(1H, brs)

Example 36-1

The following compound was obtained in a similar manner to that of Example 34-1.

methyl (2E)-3-{2-[(2S)-2-[tert-butoxycarbonylamino]-5-amino-pentanoylamino]phenyl}propanoate

(+)ESI-MS(m/z) : 394$(M+H)^+$

Example 36-2

To a solution of methyl (2E)-3-{2-[(2S)-2-[tert-butoxycarbonylamino]-5-aminopentanoylamino]phenyl}propanoate (4.34g) in dichloromethane (80mL) was added triethylamine (2.31mL) and the solution was cooled to 5℃. To the solution was added 2-chlorobenzyl chloroformate (1.86mL) at 5℃ and the mixture was stirred at the same temperature for 1hr. The solvent was removed by evaporation and the residue was partitioned between 1N HCl (80mL) and EtOAc (80mL). The organic layer was separated, washed successively with water (80mL), saturated aqueous sodium hydrogencarbonate (80mL) and brine (80mL), and dried over $MgSO_4$. Filtration followed by evaporation gave a yellow solid which was chromatographed on silica gel (eluent:hexane/EtOAc=2/1 to 3/2) to give methyl 3-{2-[(2S)-2-[tert-butoxycarbonylamino]-5-[(2-chlorobenzyloxycarbonyl)amino]pentanoylamino]phenyl}propanoate (3.62g) as a white solid.

(+)ESI-MS(m/z) : 584$(M+Na)^+$

Example 36-3

To a suspension of methyl 3-{2-[(2S)-2-[tert-butoxycarbonylamino]-5-[(2-chlorobenzyloxycarbonyl)amino]-pentanoylamino]phenyl}propanoate (3.45g) in EtOAc (15mL) was added 4N hydrogen chloride in EtOAc (45mL) and the mixture was stirred at room temperature for 1hr. The mixture was concentrated in vacuo to give methyl 3-{2-[(2S)-2-amino-5-[(2-chlorobenzyloxycarbonyl)amino]pentanoylamino]phenyl}-propanoate hydrochloride (3.11g) as a pale yellow viscous oil.

(+)ESI-MS(m/z) : 462$(M+H)^+$

Example 36-4

The following compound was obtained in a similar manner to that of Example 27-3.

methyl 3-{2-[(2S)-2-[(1-benzofuran-2-yl-carbonyl)-amino]-5-[(2-chlorobenzyloxycarbonyl)amino]pentanoylamino}phenyl]propanoate

Example 37

The following compound was obtained in a similar manner to that of Example 28.

methyl 3-{2-[(2S)-2-[(1-benzofuran-2-yl-carbonyl)-amino]-5-[(2-chlorobenzyloxycarbonyl)amino]pentanoylamino]-phenyl]propanoic acid

(-)ESI-MS(m/z) : 590$(M-H)^-$

^{1}H NMR (200MHz, DMSO-d_6, δ) : 1.59-1.99(4H, m), 2.45-2.50(2H, m), 2.78-2.85(2H, m), 3.07-3.10 (2H, m), 4.66-4.69(1H, m), 5.09(2H, s), 7.11-7.52(11H, m), 7.66-7.81(3H, m), 8.74(1H, d, J=7.6Hz), 9.61 (1H, brs), 12.1(1H, brs)

Example 38-1

The following compound was obtained in a similar manner to that of Example 36-2.

methyl 3-{2-[(2S)-2-[tert-butoxycarbonylamino]-5-[(benzyloxycarbonyl)amino]pentanoylamino]phenyl}propanoate

(+)ESI-MS(m/z) : 550$(M+Na)^+$

Example 38-2

The following compound was obtained in a similar manner to that of Example 36-3.

methyl 3-{2-[(2S)-2-amino-5-[benzyloxycarbonylamino]-pentanoylamino]phenyl}propanoate hydrochloride

(+)ESI-MS(m/z) : 428$(M+H)^+$

Example 38-3

The following compound was obtained in a similar manner to that of Example 27-3.

methyl 3-{2-[(2S)-2-[(1-methyl-1H-indol-2-yl-carbonyl)amino]-5-[benzyloxycarbonylamino]pentanoyl-aminolphenyl}propanoate

(+)ESI-MS(m/z) : 607$(M+Na)^+$

Example 39

The following compound was obtained in a similar manner to that of Example 28.

3-{2-[(2S)-2-[(1-methyl-1H-indol-2-ylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino]phenyl}propanoic acid

(-)ESI-MS(m/z) : 569$(M-H)^-$

^{1}H NMR (200MHz, DMSO-d_6, δ) : 1.59-1.91(4H, m), 2.48-2.54(2H,m), 2.79-2.87(2H, m), 3.05-3.10(2H, m), 3.98(3H, s), 4.55-4.66(1H, m), 5.01(2H, s), 7.07-7.35(13H, m), 7.53(1H, d, J=8.3Hz), 7.65(1H, d, J=7.9Hz), 8.62(1H, d, J=7.6Hz), 9.56(1H, brs), 12.1(1H, brs)

Example 40

The following compound was obtained in a similar manner to that of Example 27-3.

methyl 3-{2-[(2S)-2-[(2-quinolinylcarbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino]phenyl}propanoate

(+)ESI-MS(m/z) : 605$(M+Na)^+$

Example 41

To a suspension of methyl 3-{2-[(2S)-2-[(2-quinolinyl-carbonyl)amino]-5-[benzyloxycarbonylamino]pentanoylamino]-phenyl}propanoate (100mg) in EtOH (2.0mL) was added 1N NaOH (0.343mL) and the mixture was refluxed for 10min. The resulting solution was allowed to cool to room temperature, stirred for 16hrs, and concentrated in vacuo. The residual solid was dissolved in EtOH (2.0mL) and the solution was stirred at room temperature for 2hrs. The resulting precipitates were collected by filtration, washed with EtOH, and dried under reduced pressure at 60℃ to give sodium 3-{2-[(2S)-2-[(2-quinolinylcarbonyl)amino]-5-[benzyloxycarbonyl-amino]pentanoylamino]phenyl}propanoate (79.3mg) as a white solid.

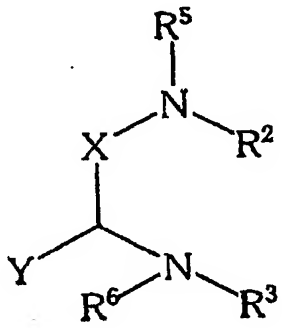
(-)ESI-MS(m/z) : 567$(M-Na)^-$

^{1}H NMR (200MHz, DMSO-d_6, δ) : 1.55-1.58(2H, m), 1.95-2.06(2H, m), 2.27-2.30(2H, m), 2.73-2.74(2H, m), 3.12-3.14(2H, m), 4.86-4.88(1H, m), 4.98(2H, s), 7.00-7.32(8H, m), 7.70-7.90(4H, m), 8.11(1H, d, J=8.1 Hz), 8.21(2H, d, J=8.5Hz), 8.61(1H, d, J=8.5Hz), 9.01(1H, d, J=8.4Hz), 13.1(1H, brs)

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula (I):



(I)

wherein

Y is

(1) lower alkyl, or

(2) Z-(CH_2)n-,

{wherein

Z is

(1) aryl, or

(2) R^1-CO-NR^4-

(wherein

R^1 is (1) aryl, heterocyclic group, heterocyclic(lower)alkoxy, ar(lower)alkyl, or ar(lower)alkoxy, each of which may be substituted with one or more substituent(s) selected from the group consisting of

(a) halogen,

(b) hydroxy, and

(c) lower alkyl, or

(2) lower alkoxy, and

R^4 is hydrogen, or lower alkyl); and

n is an integer of 1, 2, 3, 4, 5 or 6};

R^2 is (1) ar(lower)alkyl, lower alkyl, or
lower alkylthio(lower)alkyl, each of which may be substituted with one or more substituent(s) selected from the group consisting of
(a) carboxy,
(b) carboxy(lower)alkyl,
(c) amidated carboxy,
(d) esterified carboxy, and
(e) heterocyclic group,
or
(2) aryl which may be substituted with aryl, lower alkyl, lower alkylamino, lower alkoxy(lower)alkyl, lower alkylthio(lower)alkyl, lower alkylamino-(lower)alkyl, lower alkoxy, lower alkenyl, or lower alkylthio, each of which may be further substituted with one or more substituent(s) selected from the group consisting of
(a) carboxy,
(b) amidated carboxy,
(c) esterified carboxy, and
(d) heterocyclic group;

R^3 is (1) Q-R^7,
[wherein
Q is -CO- or -SO_2-,
R^7 is (a) heterocyclic group which may be substituted with
lower alkyl(s),
aryl(s) which may be substituted with halogen(s), or
halogen(s),
(b) cyclo(C_3-C_8)alkyl,
(c) aryl which may be substituted with
lower alkyl(s),

aryl(s),
halogen(s),
lower alkoxy(s),
aryloxy(s), or
hydroxy(s),

(d) lower alkyl which may be substituted with
cyclo(C_3-C_8)alkyl(s),
aryl(s) which may be substituted with
aryl(s), or
heterocyclic group(s),

(e) lower alkenyl which may be substituted with
aryl(s), or
heterocyclic group(s),

(f) amino which may be substituted with
aryl(s) which may be substituted with
aryl(s), or
heterocyclic group(s),

or

(g) aryloxy(s)],

or

(2) lower alkyl which may be substituted with
aryl(s) which may be substituted with aryl(s), or
heterocyclic group(s);

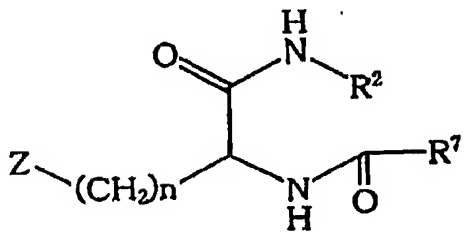
R^5 and R^6 are independently hydrogen or lower alkyl; or

R^6 and Y may be linked together to form $-(CH_2)m-$,
wherein m is an integer of 2, 3, 4 or 5; and

X is $-CO-$, or $-(CH_2)k-$;
wherein k is an integer of 1, 2 or 3,

or a pharmaceutically acceptable salt thereof.

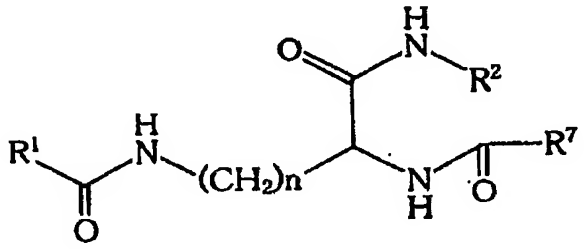
2. A compound of claim 1 having the formula (Ia):



(Ia)

wherein R^2, R^7, n and Z are as defined above.

3. A compound of claim 1 having the formula (Ib):

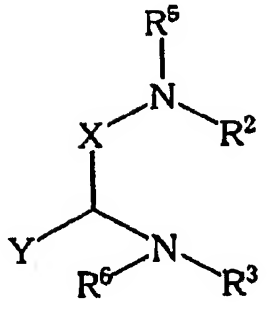


(Ib)

wherein R^1, R^2, R^7 and n are as defined above.

4. A compound of claim 3,
wherein
R^1 is ar(lower)alkoxy;
n is an integer of 1, 2, 3, 4 or 5;
R^2 is lower alky, or
aryl which may be substituted with carboxy(lower)-
alkyl;
R^7 is heterocyclic group which may be substituted with substituted with lower alkyl.

5. A process for preparing the compound of the formula (I):



(I)

wherein

Y is

(1) lower alkyl, or

(2) Z-$(CH_2)n$-,

{wherein

Z is

(1) aryl, or

(2) R^1-CO-NR^4-

(wherein

R^1 is (1) aryl, heterocyclic group, heterocyclic(lower)alkoxy, ar(lower)alkyl, or ar(lower)alkoxy, each of which may be substituted with one or more substituent(s) selected from the group consisting of

(a) halogen,

(b) hydroxy, and

(c) lower alkyl, or

(2) lower alkoxy, and

R^4 is hydrogen, or lower alkyl); and

n is an integer of 1, 2, 3, 4, 5 or 6};

R^2 is (1) ar(lower)alkyl, lower alkyl, or lower alkylthio(lower)alkyl, each of which may be

substituted with one or more substituent(s) selected from the group consisting of

(a) carboxy,

(b) carboxy(lower)alkyl,

(c) amidated carboxy,

(d) esterified carboxy, and

(e) heterocyclic group,

or

(2) aryl which may be substituted with aryl, lower alkyl, lower alkylamino, lower alkoxy(lower)alkyl, lower alkylthio(lower)alkyl, lower alkylamino-(lower)alkyl, lower alkoxy, lower alkenyl, or lower alkylthio, each of which may be further substituted with one or more substituent(s) selected from the group consisting of

(a) carboxy,

(b) amidated carboxy,

(c) esterified carboxy, and

(d) heterocyclic group;

R^3 is (1) Q-R^7,

(wherein

Q is -CO- or -SO_2-,

R^7 is (a) heterocyclic group which may be substituted with

lower alkyl(s),

aryl(s) which may be substituted with halogen(s), or

halogen(s),

(b) cyclo(C_3-C_8)alkyl,

(c) aryl which may be substituted with

lower alkyl(s),

aryl(s),

halogen(s),

lower alkoxy(s),

aryloxy(s), or
hydroxy(s),

(d) lower alkyl which may be substituted with
cyclo(C_3-C_8)alkyl(s),
aryl(s) which may be substituted with
aryl(s), or
heterocyclic group(s),

(e) lower alkenyl which may be substituted with
aryl(s), or
heterocyclic group(s),

(f) amino which may be substituted with
aryl(s) which may be substituted with
aryl(s), or
heterocyclic group(s),

or

(g) aryloxy(s),

or

(2) lower alkyl which may be substituted with
aryl(s) which may be substituted with aryl(s), or
heterocyclic group(s);

R^5 and R^6 are independently hydrogen or lower alkyl; or

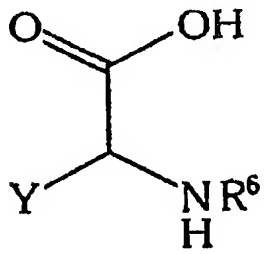
R^6 and Y may be linked together to form -(CH_2)m-,
wherein m is an integer of 2, 3, 4 or 5; and

X is -CO-, or -(CH_2)k-;
wherein k is an integer of 1, 2 or 3,

or a pharmaceutically acceptable salt thereof,

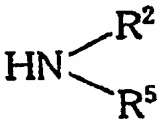
which comprises,

(1) reacting a compound (IIa):



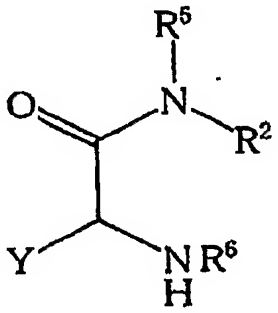
(IIa)

(wherein R^6 and Y are each as defined above), or its reactive derivative at the carboxy group or the salt thereof, with a compound (IIIa):



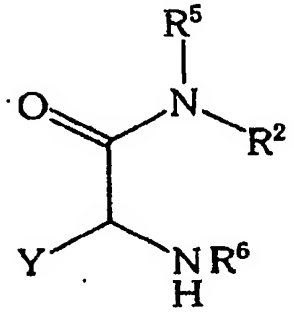
(IIIa)

(wherein R^2 and R^5 are each as defined above), or its reactive derivative at the amino group or the salt thereof to give a compound (IVa):



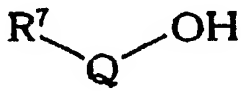
(IVa)

(wherein R^2, R^5, R^6,and Y are each as defined above), or its salt [step a]; and
reacting the compound (IVa):



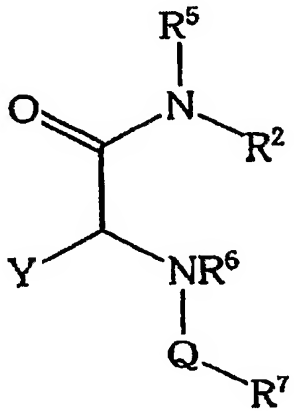
(IVa)

(wherein R^2, R^5, R^6,and Y are each as defined above), or its salt, with a compound (V):



(V)

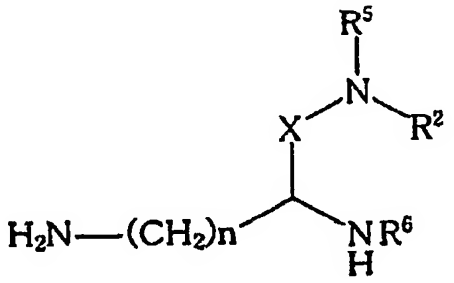
(wherein R^7 and Q are each as defined above), or its reactive derivative at the carboxy group (in case of Q is –CO-)/the sulfo group (in case of Q is -SO_2-),or the salt thereof to give a compound (Ia-1):



(I a–1)

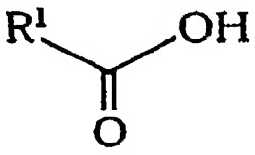
(wherein R^2, R^5, R^6, R^7, Y and Q are each as defined above),

(2) reacting a compound (IIb):



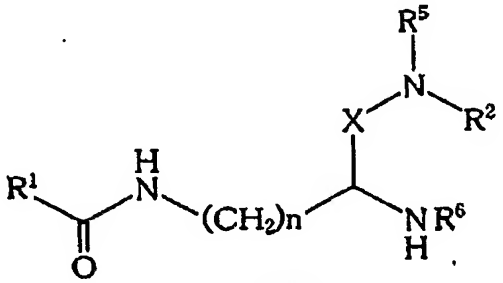
(IIb)

(wherein R^2, R^5, R^6, n and X are each as defined above), or its reactive derivative at the amino group or the salt thereof, with a compound (IIIb):



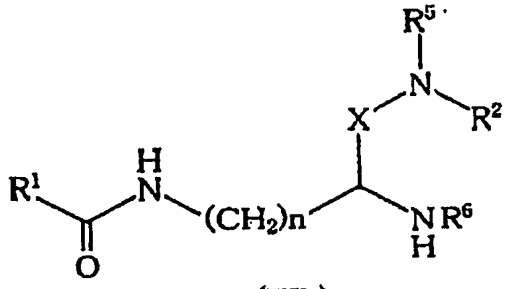
(IIIb)

(wherein R^1 is as defined above), or its reactive derivative at the carboxy group or the salt thereof to give a compound (IVb):



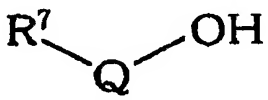
(IVb)

(wherein R^1, R^2, R^5, R^6, n and X are as defined above), or its salt; and
reacting the compound (IVb):



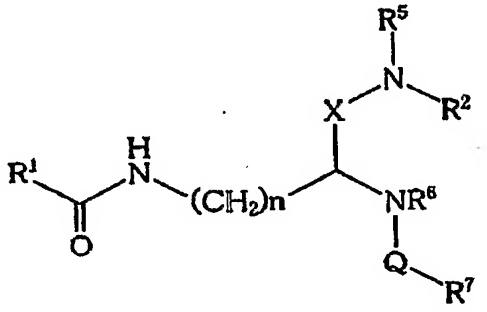
(IVb)

(wherein R^1, R^2, R^5, R^6, n and X are as defined above), or its salt, with a compound (V):



(V)

(wherein R^7 and Q are as defined above), or its reactive derivative at the carboxy group (in case of Q is –CO-)/the sulfo group (in case of Q is -SO_2-),or the salt thereof to give a compound (Ib-1):

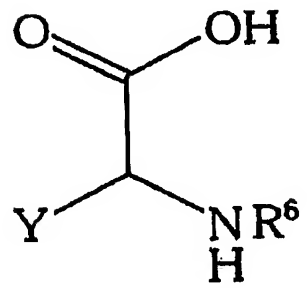


(I b–1)

(wherein R^1, R^2, R^5, R^6, R^7, n and X are as defined above),

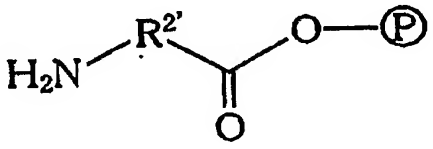
or

(3) reacting a compound (IIa):



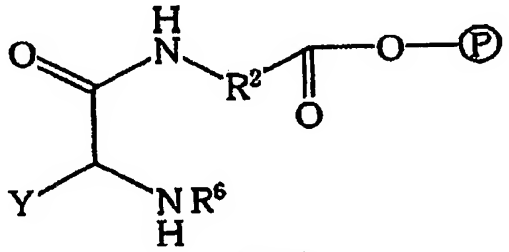
(IIa)

(wherein R^6 and Y are each as defined above), or its reactive derivative at the carboxy group or the salt thereof, with a resin-bound compound (IIIc):



(IIIc)

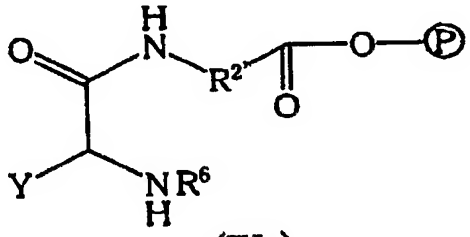
(wherein
$R^{2'}$ is
(1) ar(lower)alkyl, lower alkyl,
lower alkylthio(lower)alkyl, or
(2) aryl which may be substituted with
aryl, lower alkyl, lower alkylamino,
lower alkoxy(lower)alkyl,
lower alkylthio(lower)alkyl,
lower alkylamino(lower)alkyl, lower alkoxy,
lower alkenyl, or lower alkylthio,
Ⓟ is polymer),
or its reactive derivative at the amino group or the salt thereof to give a compound (IVc):



(IVc)

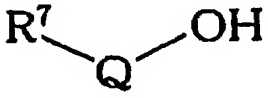
(wherein $R^{2'}$, R^6, Y and Ⓟ are as defined above), or its salt;

reacting the compound (IVc):



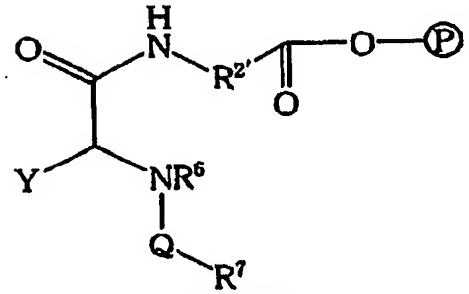
(IVc)

(wherein $R^{2'}$, R^6, Y and Ⓟ are as defined above), or its salt, with a compound (V):



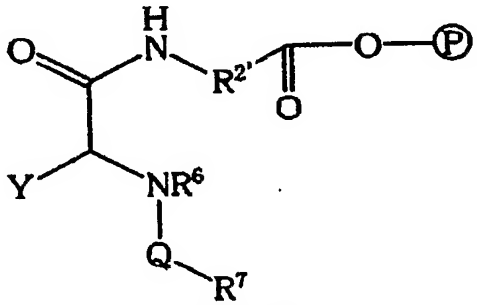
(V)

(wherein R^7 and Q are as defined above), or its reactive derivative at the carboxy group (in case of Q is –CO-)/the sulfo group (in case of Q is -SO_2-), or the salt thereof to give a compound (Ia-2'):



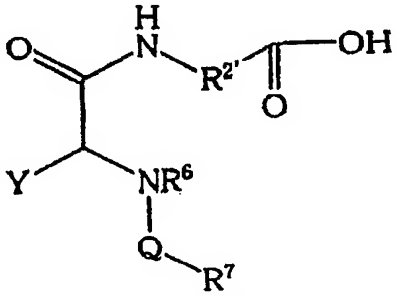
(I a-2')

(wherein $R^{2'}$, R^6, R^7, Q, Y and Ⓟ are as defined above), or its salt; and
subjecting the compound (Ia-2'):



(I a-2')

(wherein $R^{2'}$, R^6, R^7, Q, Y and Ⓟ are as defined above), or its salt to a cleavage reaction of the resin to give a compound (Ia-2):



(I a-2)

(wherein $R^{2'}$, R^6, R^7, Q and Y are as defined above), or its salt.

6. A compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

7. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

8. A use of a compound of claim 1 as a medicament.

9. A use of a compound of claim 1 as an agonist or an antagonist of PGE_2-sensitive receptor.

10. A method for treating or preventing PGE_2 mediated diseases which comprises administering an effective amount of a compound of claim 1 to human beings or animals.

11. A method for treating or preventing kidney dysfunction, inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, allergic disease, cancer or neurodegenerative diseases which comprises administering an effective amount of a compound of claim 1 to human beings or animals.

12. A use of a compound of claim 1 for the manufacture of a medicament for treating or preventing PGE_2 mediated diseases in human beings or animals.

13. A use of a compound of claim 1 for the manufacture of a medicament for treating or preventing kidney dysfunction, inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, allergic disease, cancer or neurodegenerative diseases which comprises administering an effective amount of

a compound of claim 1 to human beings or animals.

DATED this 22nd day of December 2003

Fujisawa Pharmaceutical Co., Ltd.

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